

Memo

PLAINTIFFS' TRIAL EXHIBIT
 00 Civ. 8029 (SHS)
 01 Civ. 2109 (SHS)
 01 Civ. 8117 (SHS)

PTX 498

to: Dr. T. Krishnamurphy
 cc: Dr. T.M. Ast
 Mr. M. Levy

from: Mr. B. Oshlack

dept: Pharmaceutical
 Development

subject: Codeine Contin

date: October 13, 1987

As per your request, the following is a brief summary of the developmental work for the above product.

The initial concept was to develop a controlled release tablet of Codeine Phosphate 80mg (equivalent to 60mg codeine alkaloid), to be used for a twice daily dosage. It was decided to use the patented contin system as the mechanism for the controlled release delivery. This system uses the combination of a cellulose and a higher aliphatic alcohol as the retarding mechanism within the matrix tablet.

An initial tablet formula was developed using quantities of cellulose and higher aliphatic alcohol that have been seen to be effective in retarding some other drug molecules in matrix tablets.

This first formula was as follows:

33 | 4

mg Per Tablet

Codeine Phosphate	80.0mg
Lactose	20.0mg
Hydroxyethylcellulose	8.0mg
Cetostearyl alcohol	20.0mg
Talc	2.5mg
Magnesium stearate	1.3mg
	131.8mg

Deposition Exhibit
 Purdue et al v Endo et al
 Nos. 00 Civ. 8029 (SHS),
 01 Civ. 2109 (SHS), 01 Civ. 8117 (SHS)

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Purdue Frederick Research Center

99-101 Saw Mill River Road, Yonkers, NY 10701 • Tele # (914) 968-6000 • Fax # (914) 968-6000 Ext. 603

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The lactose was used as a dilutent and the talc and magnesium stearate are lubricants.

Tablets were compressed and dissolution conducted in the USP basket/apparatus 100 rpm in simulated gastric fluid for the first hour and thereafter in simulated intestinal fluid. All subsequent dissolution testing was conductd under the same conditions.

The dissolution was as follows:

532 (533) | 21

* Codeine

Dissolved

Hours

0.5	43.0
1.0	58.3
2.0	81.9
3.0	95.8
4.0	100.0
5.0	100.0

Since the dissolution was so fast, it was thought that the dissolution could be retarded further by:

1. Increasing the quantities of retarding materials and
2. Using the less water soluble codeine alkaloid.

Hence, the following tablet formula was investigated:

533 | 16
mg/Tablet

Codeine alkaloid (anhydrous)	60.0mg
Lactose	20.0mg
Hydroxyethylcellulose	12.0mg
Cetostearyl alcohol	32.0mg
Talc	2.5mg
Magnesium stearate	<u>1.2mg</u>
	127.7mg

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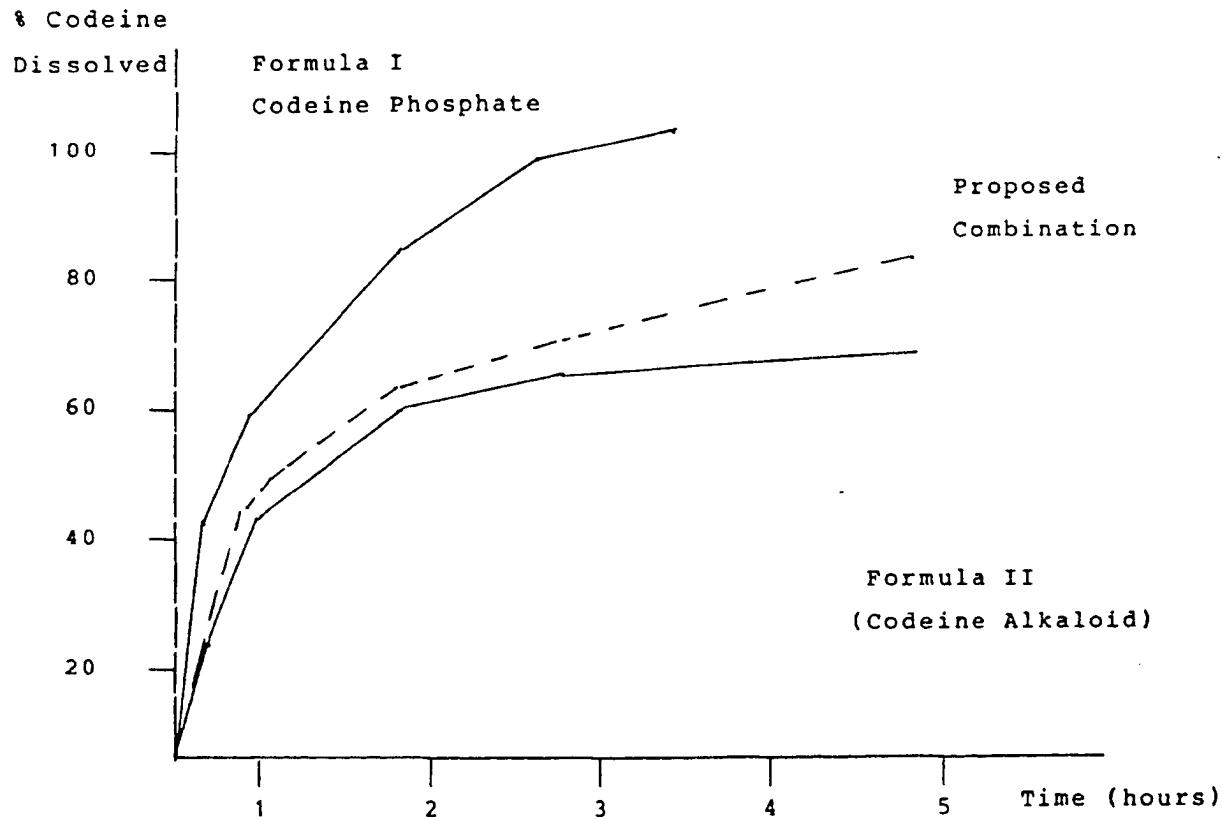
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Dissolution was as follows:

533 | 19

<u>Hours</u>	<u>% Codeine Dissolved</u>
0.5	27.7
1.0	42.8
2.0	59.3
3.0	64.8
4.0	66.2
5.0	66.2

Since the dissolution of the first formula was too fast and the dissolution of the second formula appeared to plateau at 4 hours and was too slow, it was decided to look into combining 50% of each formula.



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Thus the tablet formula then became:

Codeine Alkaloid (anhydrous)	30.0mg
Codeine Phosphate	40.0mg
Lactose	20.0mg
Hydroxyethylcellulose	10.0mg
Cetostearyl alcohol	26.0mg
Talc	2.5mg
Magnesium stearate	<u>1.3mg</u>
	129.8mg

The dissolution of this tablet was as follows:

<u>Hours</u>	<u>% Codeine Dissolved</u>
0.5	29.0
1.0	46.8
2.0	67.5
3.0	78.7
4.0	88.3
5.0	93.8
6.0	95.0

A marketing decision was then made that the codeine content of the tablet should be reduced to the equivalent of 50mg codeine alkaloid anhydrous, and that the salt used should be codeine sulphate and not codeine phosphate.

Since the previous tablet still seemed to dissolve too fast, it was decided to include the following modifications:

1. Increase the quantity of cellulose.
2. To substitute the cetostearyl alcohol with the pure stearyl alcohol, which has a longer aliphatic chain than cetyl alcohol. This would afford a slower dissolution and a harder

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tablet, but the quantity of stearyl alcohol would probably need to be reduced. With all the above considerations, the tablet formula developed was as follows:

573| C1

<u>Ingredient</u>	<u>mg/Tablet</u>
Codeine Alkaloid (anhydrous)	25.0mg
Codeine Sulphate	31.5mg(equivalent to 25mg codeine alkaloid anhydrous)
Hydroxyethylcellulose	12.0mg
Lactose	31.5mg
Stearyl alcohol	20.0mg
Talc	2.4mg
Magnesium stearate	<u>1.2mg</u> 123.6mg

Dissolution

573|17

<u>Hours</u>	<u>% Dissolved</u>
1.0	36.0
2.0	52.1
3.0	64.7
4.0	73.4
6.0	89.0

This tablet was still considered to dissolve too fast. A Medical/Marketing decision was then made that the 50mg strength would be too low, and it was decided that a 100mg codeine alkaloid anhydrous equivalent tablet would need to be made.

The previous tablet formula was thus investigated, using the same granulate, but compressing the tablets at twice the weight.

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573|14 S

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The tablet formula thus became:

573|14

<u>Ingredient</u>	<u>mg/Tablet</u>
Codeine Alkaloid (anhydrous)	50.0mg
Codeine Sulphate	63.0mg
Hydroxyethylcellulose	24.0mg (approx. 10%)
Lactose	63.0mg
Stearyl alcohol	40.0mg (approx. 16%)
Talc	4.8mg
Magnesium stearate	<u>2.4mg</u> 247.2mg

The dissolution of the tablets were as follows:

573|19

<u>Hours</u>	<u>% Codeine Dissolved</u>
1.0	27.6
2.0	43.5
3.0	50.0
4.0	56.0
6.0	69.0
Beyond six hours	Codeine still being dissolved, plateau not reached.

This formula was thus thought to show the desired release rate, however, lamination was seen during tabletting. Many experiments were subsequently conducted using various excipients to attempt to overcome the problem of lamination. Extra tablet binder was needed, however, this had to be done without affecting the

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dissolution of the tablet. A formula was finally developed using a lactose filler. Lactose has self binding properties. To compensate the extra binding of the lactose, without affecting the dissolution, the amount of Hydroxyethylcellulose was reduced from approximately 10% to 8%. The quantity of stearyl alcohol remained the same at 16% of the final tablet weight.

60517

~~51330~~

The formula thus became:

<u>Ingredient</u>	<u>mg/Tablet</u>
Codeine Alkaloid USP	52.5mg (50mg anhydrous equivalent)
Codeine Sulphate USP	63.3mg (50mg anhydrous equivalent)
Lactose	285.0mg
Hydroxyethylcellulose	45.0mg (approx. 8%)
Stearyl alcohol	90.0mg (approx. 16%)
Talc	10.8mg
Magnesium Stearate	<u>5.4mg</u>
	552.0mg

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The dissolution was as follows:

S-73-350

<u>Hour</u>	<u>% dissolved</u>
1.0	28.7
2.0	40.5
3.0	48.5
4.0	55.2
5.0	61.0
6.0	67.0
Beyond six hours	Codeine still being dissolved plateau not yet reached.

This dissolution profile was what was thought to be ideal, and there appeared to be no manufacturing problems.

Therefore several pilot batches were made to confirm reproducibility both of the manufacturing method and dissolution.

We investigated the dissolution beyond six hours, and also validated the use of water as the dissolution medium. The dissolution was:

<u>Hour</u>	<u>% Codeine dissolved</u>
1.0	26.4
2.0	38.1
3.0	47.0
4.0	55.8
6.0	68.2
8.0	86.2
10.0	94.9

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A pilot bioavailability study was conducted in 17 dogs (study # B-85-05). The results are summarized in the attached graph.

This graph summarizes the mean data of a single dose administration of a codeine contin 100mg tablet and an immediate release codeine phosphate tablet (this tablet on the graph is calculated for dose adjustment to 100mg of codeine alkaloid anhydrous). The dog study indicated the tablet might perform well as a twice daily controlled release oral tablet.

Based on these results and since a reasonable amount of stability data was established, a human bioavailability study was conducted, (study #8324-W see attached graph). This graph summarizes the mean data of a single dose administration of a codeine contin 100mg tablet and an immediate release codeine phosphate tablet (graph of this tablet is calculated dose adjusted to 100mg of codeine alkaloid anhydrous).

Since the human 14 subject bioavailability study indicated that we may have designed a controlled twice daily codeine contin tablet, it was thus decided to use this as our final formula.

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A marketing/medical decision was made that a 150mg and 200mg tablet would also be necessary for dose flexibility.

Since the codeine 100mg tablet was already large, a 150mg tablet was made by adding in 50% extra codeine alkaloid and codeine sulphate, and reducing the amount of lactose so that the final tablet weight would be approximately the same. This was done and the final tablet had the same physical characteristics as the codeine 100mg tablet.

The formula of the tablet core thus became:

<u>Ingredient</u>	<u>mg/tablet</u>
Codeine monohydrate	79.5
Codeine sulphate trihydrate	94.1
Lactose	230.0
Hydroxyethyl cellulose	45.0
Stearyl alcohol	90.0
Talc	10.0
Magnesium stearate	5.4
	<hr/>
	554.0 mg

The dissolution using the USP basket at 100 rpm in water was as follows:

<u>Hour</u>	<u>% Codeine Dissolved</u>
1	18.9
2	30.5
3	40.4
4	49.0
6	63.6

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To develop a 200mg tablet, we used the 150mg granulate and compressed this into a 200mg dosage strength.

The formula thus became:

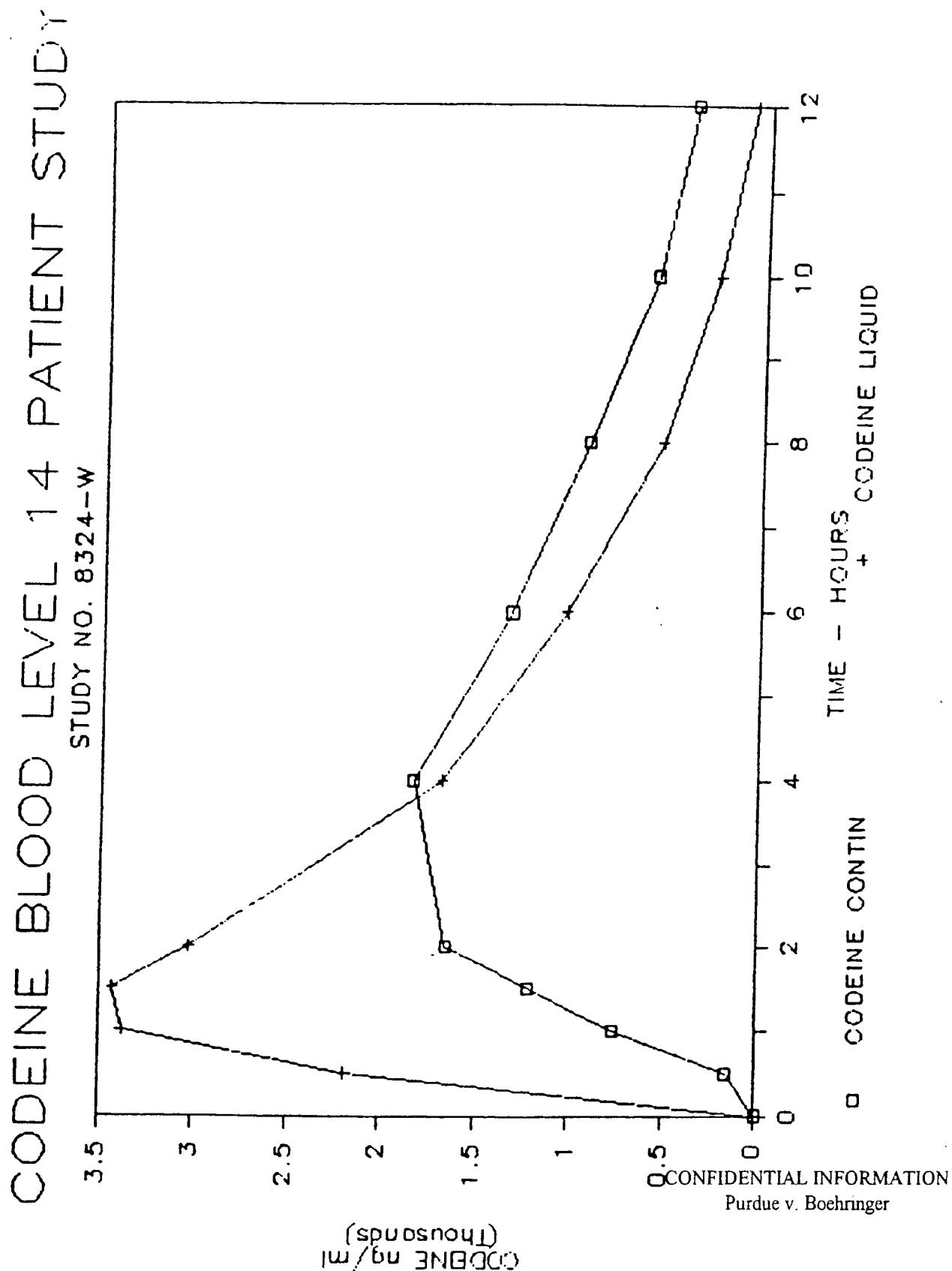
<u>Ingredient</u>	<u>Mg/tablet</u>
Codeine Monohydrate	106.0
Codeine sulphate trihydrate	125.4
Lactose	306.7
Hydroxyethyl cellulose	60.0
Stearyl alcohol	120.0
Talc	13.3
Magnesium Stearate	7.2
	738.6

The dissolution of the 200mg tablet using the USP basket apparatus at 100rpm in water was as follows:

<u>Hour</u>	<u>% Codeine Dissolved</u>
1	19.4
2	31.6
3	42.1
4	51.7
6	65.7

Since the dissolution of both the 150mg and 200mg tablet were similar to the 100mg tablet, batches of each strength were made, placed on stability, and a single dose bioavailability study was conducted, of the 100mg vs 150mg vs 200mg codeine tablet. This data is subsequently enclosed.

Attachment 1.



Attachment 2

CODINE BLOOD LEVELS IN MGS

STUDY # P-85-05

